PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ZEALAND PHARMA A/S
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PCT

06 MAY 2005

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	04.02.2005
Applicant's or agent's file reference 023-2003 WO1	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK 03/00805	25.11.2003	25.11.2002

Applicant
ZEALAND PHARMA A/S et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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Authorized Officer

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 023-2003 WO1	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/DK 03/00805	International filing date *(day/month/year)* 25.11.2003	Priority date *(day/month/year)* 25.11.2002
International Patent Classification (IPC) or both national classification and IPC C07K5/06		
Applicant ZEALAND PHARMA A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.06.2004	04.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Döpfer, K-P Telephone No. +49 89 2399-8547

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK 03/00805

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-54 as originally filed

Claims, Numbers

1-52 as originally filed

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 39-46 (IA)

   because:

   ☒ the said international application, or the said claims Nos. 39-46 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10-52
	No:	Claims	1-9
Inventive step (IS)	Yes:	Claims	10-52
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-38,47-52
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item I
Basis of the report

Re Item II
Priority

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 39-46 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: REICHARDT PETER ET AL: "Identification and Quantification of in vitro Adduct Formation Between Protein Reactive Xenobiotics and a Lysine-Containing Model Peptide" ENVIRONMENTAL TOXICOLOGY, vol. 18, no. 1, 2003, pages 29-36, XP002275870

D2: TAKASHI SEKI ET AL: "Delta-Acetyl-L-ornithyl-Beta-alanine Methyl Ester Hydrochloride, an Intermolecule Type Sweetener" AGRIC. BIOL. CHEM., vol. 54, no. 7, 1990, pages 1811-1818, XP002275871

D3: WO 02/077017 A (HOLSTEIN-RATHLOU NIELS-HENRIK ;KJOLBYE ANNE LOUISE (DK); LARSEN BJ) 3 October 2002 (2002-10-03)

D4: BAILEY PD et al.: "How to Make Drugs Orally Active: A Substrate Template for Peptide Transporter PepT1" ANGEW. CHEM. INT. ED., vol. 39, No. 3, 2000, pages 506-508 (cited in the application)

2. *Novelty and Inventive Step (Article 33(2)(3) PCT)*

2.1 The present application addresses peptides of the general formula R_2-[CHR_1-CO-NR_3]$_b$-CH(-[CH_2]$_z$-[CO]$_x$-[NH]$_y$-[CO]$_p$-[CH_2]$_q$-R_x)-CO-[NR_3-CHR_1-[CH_2]$_d$-CO]$_a$-OH/NH_2 (with R_x as hydrophobic, in particular aromatic moiety) which act as gap junction modulators with enhanced oral availability.

2.2 D2 discloses compounds (see tables V - δ-X-Orn-ß-Ala [X: Benzoyl; Salicilyl; o-Cl-Benzoyl; o-NO_2-Benzoyl] and VI - H-Orn(Bzl)-ß-Ala) which fall within the general formulae I or II of the present application. These compounds are considered pertinent for the novelty of present claims 1-9. These compounds were tested for their sweetening properties. Gap junction modulation is not mentioned or contemplated.

2.3 D3 addresses peptides with gap junction modulating activity. These peptides are of different structure, i.e. the subject-matter of the present application is novel in view of D3.

2.4 D1 discloses a compound of the formula H-Lys(2-carboxybenzoyl)-Tyr which would be pertinent for the novelty of present claims 1-9. But D1 is an intermediate document, i.e. it has been published between the priority date of the present application and the filing date. The priority claimed by the present application is assumed to be valid. Accordingly, this document does not belong to the prior art according to Rule 64.1 PCT and is therefore not to be taken into consideration for the assessment of novelty and inventive step.

2.5 The subject-matter of present claims 10-52 is not known from the prior art and is therefore novel.

2.6 D3 is regarded as to represent the closest prior art. The peptides disclosed exhibit gap junction modulating activities. The problem underlying the present application can be seen as to provide further compounds with the desired activity and improved properties. The structure of the longer peptides of D3 lets the skilled person assume that they are not useful of oral administration. The dipeptide derivatives have structures which appear not to be good templates for the PepT1 transporter which is responsible for the uptake of di- and tripeptides from the small intestine into the blood circulation (see D4). D4 gives the skilled person also some

hints for the design procedure, but there seems to be no direct hint for the design of gap junction modulators. On the other hand, there is no expectation of reasonable success when modifying the short peptides with hydrophobic residues in order to create oral availability and to maintain the gap junction modulating activity. Thus, inventive step can be acknowledged to the novel peptides as well as for the use of the known peptides as orally available gap junction modulators. This applies to present claims 10-52 in toto and to the novel subject-matter of claims 1-9.

3. *Industrial applicability (Article 33(4) PCT*

The subject-matter of present claims 1-38 and 47-52 appear to comply with the requirements of industrial applicability as stipulated in Article 33(4) PCT.

Re Item VII

Certain defects in the international application

1. Claim 27 contains a reference to the description(Table 1). According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.

Re Item VIII

Certain observations on the international application

1. Present claims 1 and 8 (and claims dependent thereon) lack clarity in that no numerical values of the variables p, q, x, y, z are given (except the provisos for p = 1 and x = 1), i.e. the scope of the claims is not clearly defined. I.e, the skilled reader does not know whether a carbonyl function in the side chain of $-[CH_2]_z-[CO]_x-[NH]_y-[CO]_p-[CH_2]_q-R_x$) is an essential feature, which could be concluded from the examples. But the whole scope of the claim encompasses also compounds without carbonyl functionality (see D2: H-Orn(Bzl)-ß-Ala). This lack of clarity is in contradiction to the requirements of Article 6 PCT.